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(54) Title: PHARMACEUTICAL COMPOSITION FOR RAPID SUSPENSION IN WATER

(57) Abstract

The invention provides a solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising (a) a drug which is substantially water-insoluble or microencapsulated; (b) a thickening or suspending agent; (c) a pharmaceutically acceptable acid; (d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d:b is from 1:1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent (b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds. A method for preparing the composition is also described.

+ DESIGNATIONS OF "SU"

It is under examination in which parts of the former Soviet Union the designation of the Soviet Union has effect.

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PHARMACEUTICAL COMPOSITION FOR RAPID SUSPENSION IN
WATER

5 The present invention relates to a pharmaceutical formulation suitable for the administration of drugs and in particular of microcapsules of drugs in a monodose sachet form, the contents of which are poured into water at the moment of use. A process for preparing the formulation is also included.

10 In the description and the claims which follow we will use mostly the terms microcapsules or microencapsulated drugs, but the present invention can also be applied to solid drug particles (powders, crystals, granules) which are insoluble or slightly soluble in water or drinkable aqueous liquids (milk, fruit juices, etc.) and of which one desires to obtain an extemporary and homogeneous suspension.

15 In the following description and claims the term:
- "microcapsule" is used to indicate drug particles, powders, crystals, granules, pellets and also liquid drops, coated in a polymeric membrane
- "microencapsulation" is generically the process used
20 for the application of a membrane
- "packet or monodose sachet" is a container which contains a single dose of drug plus the excipients of the formulation
- "thickening or suspending substances" are substances
25 which dissolve in water and which increase in density and viscosity allowing solid particles to be suspended.

Microencapsulation is a process known from some time and consists of coating substances with a continuous film based on natural or synthetic polymers.

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The processes of microencapsulation are numerous. Many of these and the relative patents are cited and described in the volumes "Microcapsules and Microencapsulation Techniques" (published in 1976) and 5 "Microcapsules and other Capsules. Advance since 1975" (published in 1979) both by M.H. Guttcho. Among the preferred processes are those described in the U.S.A. 10 patents 3,196,827 and 3,253,944 by D.E. Wurster which describe methods of mechanical coating consisting of spraying a membrane around particles using suitable apparatus, and those cited in U.S.A. patents 3,415,758, 3,155,590 and 3,341,416 which described methods of 15 chemicophysical coating based on the coacervation or separation of phases, in which the polymer making up the membrane is dissolved in a suitable solvent or vehicle of microencapsulation and the substance to be dissolved is suspended in this solution and kept in agitation.

20 The coacervation of the polymer around the substance to be coated is obtained in various manners, such as for example temperature variation, addition of another more soluble polymer in the vehicle, addition of a non solvent of the polymer constituting the membrane, etc. The membrane can be hardened and so the microcapsules 25 are separated from the vehicle for example by filtration or centrifuging and finally drying.

30 In the pharmaceutical field, microencapsulation is used to mask unpleasant tastes, for slowing down the release of the drug, for preventing irritation arising from contact of the drugs with the gastrointestinal mucosa, for protecting drugs from degradation, for separating drugs which react with each other, for transforming the

drug into a more easily used form, such as for example, converting it from a liquid state into a powder composed of microcapsules.

5 A common form of dosage for the oral administration of drugs, and especially of microencapsulated drugs, is that of monodose sachets. This moreover is the most convenient solution, if not the only one, if one must administer high doses of drugs. Monodose sachets containing microcapsules have been prepared in the 10 past, sometimes also on an industrial scale, as cited in the volume "Microencapsulation" by J.R. Nixon, Chapter 7, page 93.

15 However they often present various disadvantages due especially to the hydrorepulsion of polymers making up the microcapsule membrane (for example polymers with a base of cellulose or waxy substances) and to the specific weight of the microencapsulated substances and therefore of the said microcapsules.

20 In fact when the contents of the sachets were poured out, as usual, in a glass of water or in fruit juice or in milk, the microcapsules formed a sediment on the bottom of the glass or floated on the surface, adhering partly to the walls of the said glass. This brought a 25 notable inaccuracy to the quantity of the drug taken as well as poor acceptance by the patient who saw the particles floating or felt an unpleasant scraping sensation in the mouth or throat when swallowing the contents at the bottom of the glass where the mass of sedimented particles was found.

30 The addition of thickening substances could delay and

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maybe also eliminate the separation of the microcapsules, but in practice has given negative results because these substances tend to form lumps on contact with water which dissolve slowly and only by resorting to vigorous mechanical agitation. It was attempted to disperse these thickening substances together with other components of the formula by mixing them in the usual powder mixers. Also with this method the formation of lumps could not be avoided, but was only partly reduced.

The above mentioned difficulties were mainly solved by the invention described in Italian patent No. 1183574 which refers to a formulation, and a method for obtaining it, characterized in that:

- 15 1) a thickening agent is micronized
- 2) the thickening agent is suspended in an organic solution also containing a binding agent;
- 3) this suspension is applied by spraying it on to the surface of a substance which is easily soluble in water (sugar, sorbitol); and
- 20 4) the product obtained is dried and once mixed with the microcapsules and the flavourings is used for filling the monodose sachets.

When the contents of the sachets are poured in water and agitated, as described in the examples of the 25 patents cited, in about 1 minute a homogeneous microcapsule suspension is obtained.

In practice however it is seen that the patients, after having poured the sachet contents into water, do not 30 stir with a spoon for at least 60 seconds, but stop

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after 20-30 seconds at the most. After this time the thickener is still not sufficiently dissolved and so a homogeneous suspension is not obtained and the previously cited difficulties are only partially eliminated.

It is therefore considered necessary to find a system which reduces the mixing times. During the research carried out on this matter, most surprisingly it was found that if an acid and a base substance are added, the thickening of the liquid and the homogeneous suspension of the microcapsules is generally obtained by mixing for only 15-20 seconds.

According to the present invention there is provided a solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising

- a) a drug which is substantially water-insoluble or microencapsulated;
- b) a thickening or suspending agent;
- c) a pharmaceutically acceptable acid;
- 20 d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d : b is from 1 : 1.5 to 1 : 15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.
- 25

It is necessary however that the acid and base

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substances, are very thoroughly mixed with the thickening substance and therefore they must be soluble, or suspended in the form of micronized powder, in the organic solvent used for applying of the 5 suspension containing the thickener.

With this invention the stirring time required is reduced by 1/3 to 1/4 with respect to that of the prior art patent, making the product acceptable to the consumer and especially more easily and completely 10 assumable.

It is important to note that the addition of an acidic substance and a base to the formulation is not done to obtain effervescence; in fact this is to be avoided, as seen experimentally, the formation of bubbles of 15 carbondioxide tends to carry afloat the granules coated with the thickening agent and delays the dissolution of this, giving rise to the opposite effect to that desired.

The quantity of carbon dioxide which is formed must 20 therefore be just sufficient to keep the single particles separate from each other thus permitting a rapid hydration of the thickener.

Therefore, as determined experimentally, to obtain the desired effect, that is a rapid hydration of the 25 thickener and brief mixing times, it is necessary that the base and acid substances are:

- thoroughly mixed with said thickener; this is obtained by dissolving them in the solvent in which the thickener is suspended, or in the event that these are 30 not soluble by micronizing them to the same

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granulometry as the thickener and suspending them together with this;

-in a quantity so as not to allow effervescence but sufficient to obtaining the desired effect;

5 -in a suitable ratio with respect to each other and with the thickener.

As already cited the microcapsules can be prepared with various systems provided that the membrane which coats the drug to be constituted by a suitable polymer for 10 pharmaceutical use.

The microcapsules will usually be comprised in weight of 3% to 50% polymer and from 50% to 97% drug. The polymer constituting the membrane must be permeable or soluble in the gastrointestinal juices in order to 15 allow the release of the drug and its absorption.

The preferred polymer used is ethylcellulose, but as an illustrative and not limiting example polymers can also be cited such as for example polyacrylates, polymethacrylates, polyvinylchloride, polyvinylalcohol, 20 polyethylene, polyamides, polysiloxanes, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose acetate succinate, cellulose acetate trimellitate, copolymers of maleic acid, derivatives of phthalic acid, and also polymers 25 of natural origin such as gelatine, arabic gum and Shellac.

With regard to the drugs contained in the microcapsules, any pharmacologically active substance whether in a liquid or powdery form, crystalline or 30 granular form can be coated with polymeric membrane

resorting to a suitable microencapsulation method. As an illustrative but not limiting example the following drugs are cited: theophylline, aminophylline, acetylsalicylic acid, paracetamol, ibuprofen, 5 cimetidine, dextromethorphan HBr, noscapine HCl, phenylephrine HCl, sodium dichloxacillin, sodium flucloxacillin, bacampicillin, metochlopramide, pseudoephedrine, ambroxol HCl.

With regard to the quantity of the acid and base 10 substances to be used it is preferable that the weight ratio between the sum of the quantities of these substances, acid or base, and the thickener is included between 1:1.5 and 1:15.

However with regard to the proportion to be used 15 between the acid and base substances it is preferable that the weight ratio of the acid and base substances is included between 1:0.5 and 1:1.5.

Now the process which is the object of the invention is described. This consists of dispersing the thickening 20 substance in the middle of the other components and preferably, but not limitatively, in sweetening agents, in a manner such that when the content of the monodose sachet is poured into water or in another aqueous medium there is a rapid dissolution of the thickening 25 agent which, in 15-20 seconds confers sufficient viscosity to the medium to maintain the microcapsules in a homogeneous suspension in order to avoid the formation of lumps and especially separation of the microcapsules (floating and sedimentation).

30 The invention includes a method of preparing a

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pharmaceutical composition as described above comprising mixing b) a thickening or suspending agent, c) a pharmaceutically acceptable acid, d) a pharmaceutically acceptable base selected from 5 carbonates and bicarbonates and a) a water insoluble or microencapsulated drug wherein the ratio of c + d : b is from 1 : 1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed 10 with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

The preferred process consists substantially of the following operations:

- 15 1) micronise, grind or anyway use the thickening substances with a granulometry less than 150 μm or better 75 μm ;
- 2) micronise, grind or anyway use an acid or base substance, not soluble in the solvent with the same granulometry as the thickening substance;
- 20 3) suspend the thickening substance, in fine powder, in a solvent containing a binder; the thickener must be insoluble or at least only slightly soluble in the solvent in which the binding substance is dissolved; this, in turn, as well as obviously being soluble in the solvent, must also be soluble in water in order to "bind" the particles of the thickener to the support, but also to liberate them rapidly once in contact with the water;
- 25 4) suspend or dissolve the base and acid substances, in the suspension cited in the previous point;
- 30 5) apply the suspension thus obtained to granules

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or crystals of one or more components of the formulation to put in the monodose sachet.

Crystals or granules of one of the components of the formulation are placed in a suitable mixer, for example a planetary mixer, a coating pan, horizontal controrotating ball mixer, a discontinuous mixer with vortex centrifuge, or similar. Preferably a sweetener is used for this is or another water soluble excipient just as other mixtures of the various components of the formulation can be used.

The suspension described in points 3) and 4) is then poured slowly or sprayed in the mixer in one or two phases. They are mixed in order to obtain a homogeneous distribution of the suspension around the granules or crystals of the solid excipient(s).

6) The product thus obtained is dried in an oven or in a fluid or in the said mixer. The solvent evaporates and the particles of thickener remain 'stuck' and homogeneously dispersed around the granules or crystals of solid excipient(s).

20

The product obtained is finally sieved.

As thickening substances of possible use, the following are cited as an illustrative but not limiting example: alginates, carragenine, agar-agar, tragacanth gum, xanthan gum, guar gum, carruba gum, karaya gum, modified corn starch, carboxymethyl cellulose, crystalline cellulose alone or in combination with other hydrocolloids (e.g. AVICEL RC-591 of FMC

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Corporation). As binders the following are cited as
illustrative but not limiting examples;
methylcellulose, hydroxypropylmethylcellulose,
hydroxyethylcellulose, hydroxy-propylcellulose,
5 hydroxybutylcellulose, polyethyleneglycols,
polyvinylalcohols, polyvinylpyrrolidone, gelatine,
starches, modified starches, arabic gum.

As the inert excipients, to which the suspension
containing the thickener can be applied, the following
10 are cited as an illustrative but not limiting example,
sucrose, lactose, fructose, mannitol, anhydrous
sorbitol, maltodextrine, glycine, alanine,
pentaerythrite.

15 As the acid substances, the following are cited as an
illustrative but not limiting examples: tartaric acid,
citric acid, maleic acid, ascorbic acid, fumaric acid.

20 As the base substances, the following are cited as an
illustrative but not limiting example: sodium
bicarbonate, potassium bicarbonate, sodium carbonate
and other water soluble carbonic acid salts.

25 To facilitate the water penetration one can also add a
surfactant; cited as an illustrative but not limiting
example are: sodium dioctylsulfosuccinate, sodium
laurylsulphate, various esters of sorbitol and
sorbitans with fatty acids etc.

The surfactant can be added in any phase of the
operation, even if it is preferable to add it in phase
3) of the above described process, or mix it in a
micronized form with the other solid excipients.

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5 The monodose sachets can be made in various materials, but that preferred, since it gives greater guarantee of impermeability, is aluminium foil together with paper and with a film of atoxic plastic and heat sealed material.

10 The monodose sachets are filled with a suitable machine using a loading tower in which the microencapsule mixture of the drug, the granules prepared with the above described process and the other excipients necessary for the final formulation, for example flavourings and colours are placed. Preferably however, for an improved dosage precision, machines with a double loading tower are used in which the microcapsules of the drug and the mixture of the other 15 excipients are put into the sachet separately.

The following examples must be considered simply as illustrative of the procedure of this invention, without considering them as at all limiting of the object and scope of the said procedure.

20 EXAMPLE I

A) Preparation of the suspended granules

Place 750 g of 95% ethyl alcohol in a 2 litre beaker.

25 Add 51g of polyvinylpyrrolidone K30, 3g of acid saccharin, 51g of citric acid and keep stirring until completely in solution. Add, still stirring, 69g of micronised sodium bicarbonate (granulometry less than 75 μ m) and 210g of xanthan gum having a granulometry less than 75 μ m. Stir until a homogeneous suspension is

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obtained.

Apply this suspension to the surfaces of the sorbitol granules having a granulometry less than 700 μ m.

5 To carry out this operation the suspension is poured on 2616g of sorbitol granules placed in a counter-rotating horizontal ball mixer.

Dry the granulate for 14 hours at about 40°C in a ventilation cupboard and sieve through a 700 μ m mesh.

B) Preparation of the Monodose Sachets.

10 In a cube mixer, homogeneously mix 2000g of the granules obtained in a) with 912g of granulated sorbitol and 88.2g of microcapsules of ambroxol HCl having an ethylcellulose membrane and titre of 850mg/g.

15 Divide the mixture in monodose sachets of paper/aluminium/heat sealed polythene.

3000mg of mixture contain 75mg of ambroxol HCl.

C) The content of a sachet is poured in half a glass of water (about 50ml) and stirred with a teaspoon for about 15 seconds obtaining a homogeneous suspension 20 suitable for taking.

EXAMPLE 2

A) Preparation of the suspended granules.

In a 2 litre beaker, place 1600ml of 95% ethyl alcohol.

25 Add 72g of polyvinylpyrrolidone K30, 4.5g of acid saccharin, 77.7g of tartaric acid and stir until completely in solution.

30 Add, still stirring, 55g of ground potassium bicarbonate (granulometry less than 50 μ m) and 1452g of guar gum (granulometry less than 50 μ m).

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Stir until a homogeneous suspension is obtained.

Apply this suspension to the surfaces of granulated lactose having a granulometry less than 700 μm .

5 To carry out this operation place 700g of granulated lactose in a laboratory mixer and mix with the suspension obtained previously.

Allow the granulate to dry under cover and sieve through a 700 μm mesh.

10 Dry the granulate for 14 hours at about 40°C in a ventilation cupboard and eliminate the fraction at less than 250 μm .

B) Preparation of the monodose sachets

15 In a V mixer place 250g of the granulate obtained in A), 50g of granulated lactose, 97g of ibuprofen microcapsules having a cellulose acetate phthalate membrane and titre of 909mg/g, 1g of talc and 2g of mint flavouring.

20 Divide the mixture into monodose sachets made of paper/aluminium/heat sealed polythene.

4g of the mixture contain 800mg of ibuprofen.

C) The content of a sachet was poured into half a glass of water (about 50ml) and stirred with a teaspoon for about 25 seconds obtaining a homogeneous suspension
25 suitable to be taken.

EXAMPLE 3

A) Preparation of the suspended granules.

In a 5 litre beaker, place 2000ml of 95% ethyl

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alcohol.

Add 120g of polyvinylpyrrolidone K30, 72g of anhydrous citric acid and stir until a complete solution is obtained.

5 Add, still stirring, 48g of ground sodium bicarbonate (granulometry less than 100 μ m) and 1200g of xanthan gum (granulometry less than 100 μ m).

Stir until a homogeneous suspension is obtained.

10 Apply this suspension to the surfaces of the sucrose granules having a granulometry between 210-700 μ m.

To carry out this operation the suspension was sprayed on 8140g of sucrose granules put in a flat-bottomed laboratory coating pan.

15 Dry the granulate in said coating pan and sieve through a 850 μ m.

B) Preparation of monodose sachets.

20 In a cube mixer, place 2000g of granules obtained in A), 620g of granulated sucrose, 880g of microcapsule potassium chloride (titre 860mg/g, ethylcellulose membrane, P.R. 8:1) 0.5g of talc, 1.5g of cherry flavouring.

Divide the mixture into monodose sachets made of paper/aluminium/thermosealed polythene.

25 3500mg of mixture contain 750mg of potassium chloride.

30 C) The contents of a sachet were poured into half a glass of water (about 50ml) and stirred with a teaspoon for about 15 seconds obtaining a homogeneous suspension suitable to be taken.

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EXAMPLE 4

A) Preparation of the suspended granules.

Place 250ml of 95% ethyl alcohol in a 1 litre beaker.

5 Add 20g of polyvinylpyrrolidone K30, 1g of acid saccharin, 12.5g of anhydrous citric acid and stir until completely in solution.

10 Add, while still stirring, 16.25g of ground sodium bicarbonate (granulometry less than 50 μm) and 110g of xanthan gum (granulometry less than 50 μm).

15 Apply this suspension to the surfaces of the sorbitol granules having a granulometry less than 700 μm .

Stir until a homogeneous suspension is obtained.

15 To carry out this operation the suspension was poured on 840g of sorbitol granules put in a laboratory mixer. Dry the granules in a fluid bed and sieve through a 850 μm mesh and eliminate the portion smaller than 250 μm .

20 B) Preparation of the monodose sachets.

In a cube mixer, place 2000g of the granules obtained in A), 1190g of granulated sorbitol, 350g of theophylline MIC (titre 860mg/g, ethylcellulose membrane, P.R. 8:1), 10g of talc, 50g of strawberry flavouring.

25 Divide the mixture into monodose sachets made of paper/aluminium/thermosealed polythene.

3500mg of mixture contain 300mg of theophylline.

30 C) The contents of a sachet were poured into half a glass of water (about 50ml) and stirred with a teaspoon for about 15 seconds obtaining a homogeneous suspension suitable to be taken.

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EXAMPLE 5

5 To check the advantage of the method described in this invention with respect to the granules which are object of the Italian patent no 1183574, a granular suspension was prepared using the same method and the same excipients cited in example 3 in point A) but without citric acid and without sodium bicarbonate.

10 The monodose sachets were prepared using the same method and the same composition described in example 3 in point B).

15 The contents of these sachets were poured into the same quantity of water described in example 3 in point C) and mixed with a spoon: to obtain a homogeneous suspension it is necessary to mix for 55-75 seconds, that is a 3-4 times longer than that in example 3.

EXAMPLE 6

20 To check the advantage of the method described in this invention with respect to the monodose sachets prepared according to the usual methods, the excipients sachets prepared according to the usual methods, the excipients described in example 3, point A) i.e. 260g of citric acid, 340g of sodium bicarbonate and 1090g of xanthan gum, are granulated with 170g of polyvinyl-pyrrolidone in an alcoholic solution in order to obtain granules 25 smaller than 700 μ m.

This granulate was mixed with 8140g of sucrose having a

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granulometry between 210 and 700 μm .

The monodose sachets were prepared with the same method and the same composition described in example 3, point B).

5 The contents of these sachets were poured in the same quantity of water described in example 3, point C) and mixed with a spoon. It was found that to obtain a suspension of the microcapsules it is necessary to mix for more than 2 minutes and furthermore this suspension
10 is not homogeneous but some lumps are present due to an irregular dispersion and hydration of the thickener.

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CLAIMS

1. A solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising
 - a) a drug which is substantially water-insoluble or microencapsulated;
 - b) a thickening or suspending agent;
 - c) a pharmaceutically acceptable acid;
 - d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d : b is from 1 : 1.5 to 1 : 15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.
2. A composition as claimed in Claim 1, wherein the weight ratio of c + d : b is from 1 : 1.5 to 1 : 5.
3. A composition as claimed in Claim 1 or Claim 2, wherein the weight ratio of c : d is from 1 : 0.5 to 1 : 1.5.
4. A composition as claimed in Claim 1, 2 or 3 wherein the acid is selected from tartaric, citric, pyruvic, malic, ascorbic and fumaric acids.
5. A composition as claimed in any one of Claims 1 - 4, wherein the carbonate or bicarbonate b) is selected from sodium bicarbonate, potassium bicarbonate, sodium carbonate and other water soluble carbonic acid salts.

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6. A composition as claimed in any one of the preceding claims, wherein the thickening or suspending agent is selected from alginates, carrageenin, agar-agar, tragacanth gum, xanthan gum, guar gum, carruba gum, karaya gum, modified corn starch, carboxymethylcellulose, crystalline cellulose, alone or in combination with another hydrocolloid.

7. A composition as claimed in any one of the preceding Claims, wherein the composition contains a binding agent.

8. A composition as claimed in Claim 7, wherein the binding agent is selected from methylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, polyethyleneglycol, polyvinyl alcohols, polyvinylpyrrolidone, gelatine, amides or modified amides.

9. A composition as claimed in any one of the preceding Claims incorporating one or more excipients selected from sucrose, lactose, mannitol, anhydrous sorbitol, maltodextrine, glycocoll, alanine and pentaerythrite .

10. A composition as claimed in any one of the preceding Claims including a surfactant.

11. A composition as claimed in any one of the preceding Claims wherein a microencapsulated drug is used and is selected from ibuprofen, ambroxol hydrochloride, theophylline and potassium chloride.

12. Sachets containing unit doses of a composition as claimed in any one of the preceding Claims.

13. A method for preparing a pharmaceutical composition as claimed in any one of the preceding Claims 1 - 12 which method comprises mixing b) a thickening or suspending agent c) a pharmaceutically acceptable base selected from carbonates and bicarbonates and a) a water insoluble or microencapsulated drug wherein the ratio of c + d : b is from 1 : 1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

14. A method as claimed in Claim 13, wherein the thickening or suspending agent b) has the same granulometry as the acid c) and base d).

15. A method as claimed in Claim 13 or 14, wherein the ingredients b, c and d are mixed in a non-aqueous solvent, then applied to a water soluble excipient and the mixture dried and then mixed with the drug.

16. A method as claimed in Claim 14, wherein the granulometry is less than 150 μm .

17. A method as claimed in any one of Claims 13 to 16, wherein the ingredients b, c and d are mixed to form a homogeneous suspension in a non-aqueous solvent in which a binder is dissolved and in which the ingredient b is substantially insoluble, the suspension is applied to a water soluble excipient and dried, then

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mixed with the drug.

18. A method as claimed in Claim 17, wherein the excipient is selected from sucrose, lactose, fructose, mannitol, anhydrous sorbitol, maltodextrin, glycine, alanine and pentaerythrite.

19. A pharmaceutical composition as claimed in Claim 1 substantially as hereinbefore described in any one of examples 1 to 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 91/01268

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶According to International Patent Classification (IPC) or to both National Classification and IPC
Int.Cl. 5 A61K9/50 ; A61K9/00 ; A61K9/10

II. FIELDS SEARCHED

Minimum Documentation Searched?

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

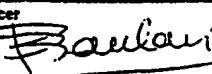
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US,A,2 125 577 (AKIYOSHI MATSUMAE) September 10, 1936 see page 1, column 1, line 1 - page 1, column 1, line 9 see page 1, column 2, line 10 - page 1, column 2, line 37 see page 2, column 1, line 3 - page 2, column 1, line 12 see claims 1-4 ---- -/-	1-6

¹⁰ Special categories of cited documents :¹⁰

- ^{"A"} document defining the general state of the art which is not considered to be of particular relevance
- ^{"E"} earlier document but published on or after the international filing date
- ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ^{"O"} document referring to an oral disclosure, use, exhibition or other means
- ^{"P"} document published prior to the international filing date but later than the priority date claimed

^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.^{"Z"} document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
3 17 SEPTEMBER 1991	- 1. 10. 91
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer BOULOIS D. 

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	<p>WO,A,8 606 626 (EURAND ITALIA SPA) November 20, 1986</p> <p>Document cited in the application</p> <p>see page 1, line 1 - page 1, line 3</p> <p>see page 3, line 27 - page 4, line 14</p> <p>see page 5, line 8 - page 5, line 29</p> <p>see page 10; example 8</p> <p>see claims</p> <p>& IT,A,1 183 574 (EURAND ITALIA SPA) November 20, 1986</p> <p>---</p>	1-13
Y	<p>US,A,3 928 252 (LLOYD E.R. ET AL) December 23, 1975</p> <p>see column 1, line 9 - column 1, line 14</p> <p>see column 3, line 10 - column 3, line 17</p> <p>see column 5 - column 6; example II</p> <p>see claims 1,3,15</p> <p>---</p>	1-13
A	<p>WO,A,8 602 834 (GERGELY G.) May 22, 1986</p> <p>see page 1, paragraph 1 -paragraph 2</p> <p>see page 4, paragraph 2 - page 6, paragraph 1</p> <p>see page 8, paragraph 1</p> <p>see page 15 - page 16; examples 8,9</p> <p>see claims 1-4</p> <p>---</p>	1-19

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

EP 9101268
SA 48877

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

17/09/91

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